Provision Translation (as of January 2026)*

Thoughts on the Use of Weight of Evidence Approach in Nonclinical Safety Evaluation (Early Consideration)

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Pharmaceuticals and Medical Devices Agency
Center for Product Evaluation

1. Background

With the development of the ICH guidelines, the safety evaluation has been performed taking into consideration the 3Rs of animal experiments (reduce, refine, replace) in the pharmaceutical development. Ethical considerations in animal experiments are increasingly demanded internationally due to growing social concern for animal welfare.

In addition, with the establishment of New Modality[1] in the safety evaluation of drugs and regenerative medical products (hereinafter referred to as "medical products") in recent years, issues concerning differences in reactivity between humans and animals (species-specific differences) and challenges in selection of appropriate animal species in the nonclinical safety evaluation have become increasingly evident. As a result, appropriate risk assessment becomes difficult in some cases of the nonclinical safety evaluation in conventional animal experiments. Furthermore, with advances in scientific technology, New Approach Methodologies (hereinafter referred to as "NAMs")[2] have been gaining attention as new scientific evaluation methods replacing or complementing animal experiments. Data acquisition that contributes to improving efficacy, safety, and pharmacokinetic predictability in humans is anticipated.

2. Objective of this Early Consideration

In view of the establishment of New Modality and the limitations of the nonclinical safety evaluation in animal experiments, all available information should be fully used to gain insights that are relevant to the safety, pharmacokinetics, etc. in humans in the development of medical products. Proactive use of the safety evaluation by the Weight of Evidence (hereinafter referred to as "WOE") approach[3] will be a useful method. NAMs may be used in combination with animal experiments as a basis for the WOE approach. Use of an evaluation method independent animal experiments is expected to promote an efficient, logical, and scientifically valid nonclinical safety evaluation and contribute to the improvement of safety prediction in humans. Based on the above background, this Early

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* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Consideration presents PMDA's thoughts on the nonclinical safety evaluation using the WOE approach including the use of data obtained from NAMs in the nonclinical safety evaluation.

Note that the thoughts presented in this document have been prepared based on the current scientific knowledge and international trends and may change as they change in the future.

3. Actions related to the use of the WOE approach in the nonclinical safety evaluation

Until now, PMDA has provided advice on nonclinical safety evaluation using the WOE approach and safety assurance in humans according to the development stage and the target disease through consultations for and reviews of individual medical products. In consideration of the above situation, PMDA will promote nonclinical safety evaluation using the WOE approach including the use of data obtained through NAMs and conduct the following activities to contribute to prompt and more accurate risk evaluation based on scientific evidence, the 3Rs, and efficient development of medical products.

- PMDA will organize thoughts on nonclinical safety evaluation of medical products using the WOE approach utilizing accumulated consultation cases on nonclinical safety evaluation using the WOE approach and discussions at the AMED research groups, academic conferences, etc.
- PMDA will discuss the use of data obtained through NAMs in nonclinical safety evaluation and its challenges with the related parties inside and outside of PMDA and consider acceptance of the data obtained through NAMs.
- PMDA will present thoughts on the specific cases of nonclinical safety evaluation using the WOE approach at academic conferences, in research papers, on the PMDA website, etc.

Through these actions, PMDA will promote the principle of 3Rs, improve the medical product safety prediction in humans, and strive to promote the development of safer and more effective medical products in collaboration with the related parties.

[Glossary]

The following terms are defined as follows in this document.

1. New Modality

Refers to classification of medical products. using new molecules and technologies that are different from those used in the conventional small molecule drugs and antibody drugs. Examples include oligonucleotide therapeutics, cell therapy products, gene therapy products, multi specific antibodies, and antibody-drug conjugates.

2. New Approach Methodologies

Tools to evaluate the efficacy, safety, and pharmacokinetics of medical products. without using the conventional animal models and encompasses all technologies and methodologies including *in silico*, *in chemico*, *in vitro*, and *ex vivo* approaches (ECHA, 2016. New approach methodologies in regulatory science. Proceedings of a scientific workshop. Helsinki: European Chemicals Agency. doi: 10.2823/543644).

3. Weight of Evidence approach

Concept or method of comprehensive evaluation combining multiple available data and information (Ministry of Health, Labour and Welfare, Ministry of Economy, Trade and Industry, Ministry of the Environment 2025. Weight of Evidence implementation manual for biodegradation assessment in CSCL risk evaluation) to draw conclusions that are not clear from a single piece of data (OECD, 2010. OECD Environment, Health and Safety Publications Series on Testing and Assessment No. 129 GUIDANCE DOCUMENT ON USING CYTOTOXICITY TESTS TO ESTIMATE STARTING DOSES FOR ACUTE ORAL SYSTEMIC TOXICITY TESTS).

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